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TITLE: Biological tissue adhesives, articles, and methods

Detail Description Paragraph (43):

[0072] After blocking at least a portion of the amine groups, the complete further functionalization is done under anhydrous conditions. At least a portion of the available carboxyl groups in the collagen support are converted into active esters using a carbodiimide in the presence of NHS, for example, as described in greater detail below. Activation of activating agents such as carbodiimides (e.g., dicyclohexyl carbodiimide (DCC)) gives O-acylisourea groups. In the presence of N-hydroxysuccinimide (NHS) or other suitable stabilizing agents, the O-acylisourea can be converted to an NHS activated carboxylic acid group, that is more stable towards hydrolysis. Thereafter the carbodiimide reagent is removed from the collagen support by rinsing the collagen support. The yielded product is then stored under essentially dry conditions.

Detail Description Paragraph (47):

[0076] As an example of an activated ester adhesive glue, in Scheme I shown below, poly(glutamic acid) is initially converted in part into an active ester (e.g., N-hydroxysuccinimide) using a carbodiimide (R.sub.1--N.dbd.C.dbd.N--R.sub.2), under anhydrous conditions. Activation of the carboxyl groups with activating agents such as carbodiimides (e.g., 1-ethyl-3-(3-dimethyl aminopropyl) carbodiimide-HCl (EDC)) gives O-acylisourea groups. In the presence of N-hydroxysuccinimide (NHS) or other stabilizing agents, the O-acylisourea can be converted to an NHS activated carboxyl group. After the introduction of active esters the obtained intermediate is either kept in an anhydrous solvent, or is dried and stored under essentially dry conditions. When the intermediate is mixed with a solution of gelatin (which includes hydrolyzed collagen), for example, spontaneous gelling occurs as a result of reaction with the free amine groups. When applied to a wound, this gel is believed to adhere to tissue via the formation of covalent bonds.

Detail Description Paragraph (49):

[0078] In an alternative embodiment as shown in Scheme II below, the pendant amine groups in gelatin can be inactivated toward amide bond formation, e.g., by acylation. Then at least a portion of the carboxyl groups are converted into an active ester (e.g., N-hydroxysuccinimide) using a carbodiimide (general formula: R.sub.1--N.dbd.C.dbd.N--R.sub.2), under anhydrous conditions. After the introduction of active esters the obtained intermediate is either kept in an anhydrous solvent, or is dried and stored under essentially dry conditions. The intermediate is then mixed with untreated gelatin in solution, thereby forming an N-hydroxysuccinimide activated gelatin, and applied to the wound. A crosslinked gel will be formed that is believed to adhere to the wound site via covalent bonds. Added water (or the moisture present in biological tissue) is typically all that is required to cause adhesion of the biological adhesive (and/or adhesive articles on which they are coated or to which they are covalently grafted) to biological tissue. 2